Complete Summary

GUIDELINE TITLE

Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents.

BIBLIOGRAPHIC SOURCE(S)

Department of Health and Human Services, Henry J. Kaiser Family Foundation. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Bethesda (MD): Department of Health and Human Services, Henry J. Kaiser Family Foundation; 2004 Mar 23. 97 p. [355 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Human immunodeficiency virus (HIV) infections (including asymptomatic, established, and acute HIV)
- Acquired immunodeficiency syndrome (AIDS)

GUIDELINE CATEGORY

Management
Treatment

CLINICAL SPECIALTY

Family Practice
Infectious Diseases
Internal Medicine
Obstetrics and Gynecology
Pediatrics
Preventive Medicine

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To use the advances in current understanding of the pathogenesis of human immunodeficiency virus (HIV) in the infected person to translate scientific principles and data obtained from clinical experience into recommendations that can be used by the clinician and patient to make therapeutic decisions

TARGET POPULATION

Adults, adolescents, and pregnant women infected with human immunodeficiency virus (HIV)

Guidance for the use of antiretroviral treatment in pediatric HIV infection is not contained in this guideline document. There are unique therapeutic and management considerations in HIV-infected children. In recognition of these differences, a separate document addresses pediatric-specific issues related to antiretroviral therapy.

INTERVENTIONS AND PRACTICES CONSIDERED

1. The use of testing for plasma human immunodeficiency virus-ribonucleic acid (HIV-RNA) levels (viral load) and $CD4^+$ T cell count in guiding decisions for therapy
2. Evaluation before initiating therapy, including complete history and physical, complete blood count, chemistry profile (including serum transaminases and lipid profile). Additional evaluation to prevent opportunistic infections, as needed.
3. Testing for antiretroviral drug resistance, including genotyping and phenotyping assays
4. Approaches to improve adherence to antiretroviral therapy including:
    - Patient-related strategies
    - Clinician and health team-related strategies
    - Regimen-related strategies
    - Directly observed therapy
    - Patient education
    - Pharmacist-based adherence encounters/clinics
5. Discontinuing and/or interrupting therapy
6. Criteria for changing therapy and alternative therapeutic options
7. Prevention counseling, including assessment and documentation of patient's knowledge and understanding of the means of HIV transmission, the patient's

HIV transmission behaviors since last encounter with health care provider, and discussion of strategies to prevent transmission

8. Antiretroviral agents:
    - Nucleoside analogue reverse transcriptase inhibitors (NRTIs):
        - Zidovudine (ZDV; AZT; Retrovir®)
        - Didanosine (ddI; dideoxyinosine; Videx®)
        - Zalcitabine (ddC; dideoxycytidine; Hivid®)
        - Stavudine (d4T; Zerit®)
        - Lamivudine (3TC, Epivir®)
        - Abacavir (ABC; Ziagen®)
        - Tenofovir disoproxil fumarate (DF) (Viread®)
        - Emtricitabine (Emtriva™)
    - Non-nucleoside reverse transcriptase inhibitors (NNRTIs):
        - Delavirdine (DLV; Rescriptor®)
        - Efavirenz (Sustiva®)
        - Nevirapine (NVP; Viramune®)
    - Protease inhibitors (PIs):
        - Indinavir (Crixivan®)
        - Nelfinavir (Viracept®)
        - Ritonavir (Norvir®)
        - Saquinavir (hard gel capsule, Invirase®, and soft gel capsule, Fortovase®)
        - Amprenavir (Agenerase®)
        - Lopinavir/Ritonavir (Kaletra®)
        - Atazanavir (Reyataz™)
    - Fusion inhibitor (FIs)
        - Enfuvirtide (Fuzeon®)

        Note: Until the results of further clinical studies are known, FIs should be reserved for patients who have failed initial regimens.

9. Note: The use of hydroxyurea is discussed in a companion document but not recommended.

MAJOR OUTCOMES CONSIDERED

- Viral load
- Immunologic function
- Adherence to treatment
- Therapy-associated adverse effects
- Quality of life
- Human immunodeficiency virus (HIV)-related morbidity and mortality

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Categories reflecting the quality of evidence supporting the recommendations:

I. At least one randomized trial with clinical results
II. Clinical trials with laboratory results
III. Expert opinion

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Strength of Recommendation

A: Strong, should always be offered

B: Moderate, should usually be offered

C: Optional

D: Should usually not be offered

E: Should never be offered

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Note from the National Guideline Clearinghouse (NGC): The updated (March 23, 2004) "Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents" includes changes to antiviral regimens recommended for treatment of HIV-1 infection in antiretroviral naive patients; new safety information regarding the risks of nevirapine-associated symptomatic hepatic events; characteristics and drug interaction information for fosamprenavir; and a new table with "Antiretroviral Dosing Recommendations for Patients with Renal or Hepatic Dysfunction."

The following provides a summary of the major recommendations presented in the guideline document. The reader is directed to the original guideline document for a detailed discussion of each of the topics presented below.

Antiretroviral regimens are complex, have serious side effects, pose difficulty with adherence, and carry serious potential consequences from the development of viral resistance because of nonadherence to the drug regimen or suboptimal levels of antiretroviral agents. Patient education and involvement in therapeutic decisions is critical. Treatment should usually be offered to all patients with symptoms ascribed to human immunodeficiency virus (HIV) infection. Recommendations for offering antiretroviral therapy among asymptomatic patients require analysis of real and potential risks and benefits. Treatment should be offered to persons who have $\leq$350 $CD4^+$ T cells/mm^3 or plasma HIV ribonucleic acid (RNA) levels of >55,000 copies/mL (by b-deoxyribonucleic acid [bDNA] or reverse transcriptase-polymerase chain reaction [RT-PCR] assays). The recommendation to treat asymptomatic patients should be based on the willingness and readiness of the person to begin therapy; the degree of existing immunodeficiency as determined by the $CD4^+$ T cell count; the risk for disease progression as determined by the $CD4^+$ T cell count and level of plasma HIV RNA; the potential benefits and risks of initiating therapy in an asymptomatic person; and the likelihood, after counseling and education, of adherence to the prescribed treatment regimen.

Treatment goals should be maximal and durable suppression of viral load, restoration and preservation of immunologic function, improvement of quality of life, and reduction of HIV-related morbidity and mortality. Results of therapy are evaluated through plasma HIV RNA levels, which are expected to indicate a 1.0 $\log_{10}$ decrease at 2 to 8 weeks and no detectable virus (<50 copies/mL) at 4 to 6 months after treatment initiation. Failure of therapy at 4 to 6 months might be ascribed to nonadherence, inadequate potency of drugs or suboptimal levels of

antiretroviral agents, viral resistance, and other factors that are poorly understood. Patients whose therapy fails in spite of a high level of adherence to the regimen should have their regimen changed; this change should be guided by a thorough drug treatment history and the results of drug-resistance testing. Because of limitations in the available alternative antiretroviral regimens that have documented efficacy, optimal changes in therapy might be difficult to achieve for patients in whom the preferred regimen has failed. These decisions are further confounded by problems with adherence, toxicity, and resistance. For certain patients, participating in a clinical trial with or without access to new drugs or using a regimen that might not achieve complete suppression of viral replication might be preferable.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

Recommendations were made by the Panel on Clinical Practices for the Treatment of Human Immunodeficiency Virus (HIV) on the basis of data from clinical trials. When clinical trial data was unavailable, recommendations were made on the basis of the opinions of persons experienced in the treatment of HIV infection and familiar with the relevant literature. The type of supporting evidence is identified for specific recommendations in the original guideline document.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Overall Benefits

The primary goals of antiretroviral therapy are maximal and durable suppression of viral load, restoration or preservation of immunologic function, improvement of quality of life, and reduction of human immunodeficiency virus (HIV)-related morbidity and mortality.

Specific Benefits

Early initiation of antiretroviral treatment in asymptomatic HIV-infected patients:

- Earlier suppression of viral replication
- Preservation of immune function
- Prolongation of disease-free survival
- Lower risk of resistance with complete viral suppression
- Possible decrease in risk for viral transmission

Delayed therapy in asymptomatic HIV-infected patients:

- Avoidance of treatment-related negative effects on quality of life and drug-related toxicities
- Preservation of treatment options
- Delay in the development of treatment resistance

POTENTIAL HARMS

Overall Harms

The risks of therapy for human immunodeficiency virus (HIV) infection include adverse effects on quality of life resulting from drug toxicities and dosing constraints; the potential, if therapy fails to effectively suppress viral replication, for the development of drug resistance, which may limit future treatment; and the potential need for continuing therapy indefinitely.

Specific Harms

Early initiation of antiretroviral therapy in the asymptomatic HIV-infected patient:

- Drug-related adverse effects on quality of life
- Drug-related serious toxicities
- Early development of drug resistance due to suboptimal viral suppression
- Risk of transmission of virus resistant to antiretroviral drugs (if suboptimal suppression)
- Limitation of future treatment options
- Unknown durability of current available therapy

Delayed therapy in the asymptomatic HIV-infected patient:

- Possible risk of irreversible immune system compromise
- Possible greater difficulty in viral suppression
- Possible increased risk of HIV transmission

Refer to the original guideline document for important and more detailed information regarding the potential risks of individual antiretroviral drugs, highly active antiretroviral therapy, and potential drug interactions.

Subgroups Most Likely to be Harmed

Women of Reproductive Age

In women of reproductive age, regimen selection should account for the possibility of planned or unplanned pregnancy. The most vulnerable period in fetal organogenesis is early in gestation, often before pregnancy is recognized. Sexual activity, reproductive plans, and use of effective contraception should be discussed with the patient. As part of the evaluation for initiating therapy, women should be counseled about the potential risk of efavirenz-containing regimens should pregnancy occur. These regimens should be avoided in women who are trying to conceive or are not using effective and consistent contraception. This counseling should be provided on a routine basis after initiation of therapy as well.

Pregnant Women

Pregnancy should not preclude the use of optimal therapeutic regimens. However, because of considerations related to prevention of mother-to-child-transmission and to maternal and fetal safety, timing of initiation of treatment and selection of regimens are different than for the nonpregnant adults or adolescents.

CONTRAINDICATIONS

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Some agents or combinations of agents are generally contraindicated due to suboptimal antiviral potency, unacceptable toxicity, or pharmacological concerns. These are summarized as follows:

- Monotherapy: All single-drug regimens are considered contraindicated because none have demonstrated potent and sustained antiviral activity. The rare exception is zidovudine (ZDV) monotherapy as part of the Pediatric AIDS Clinical Trials Group (PACTG) 076 ZDV regimen for a pregnant woman who does not meet clinical, immunologic, or virologic criteria for initiation of therapy and who has an human immunodeficiency virus ribonucleic acid (HIV RNA) <1,000 copies/mL. The goal of therapy is to prevent perinatal HIV-1 transmission. ZDV monotherapy should be discontinued immediately after delivery or combination antiretroviral therapy can be initiated if clinically indicated.
- Dual nucleoside therapy: These regimens are not currently recommended as initial therapy because none have demonstrated potent and sustained antiviral activity as compared to three-drug combination regimens. For patients previously given this treatment, it is reasonable to continue if viral suppression to less than the limit of detection is achieved and sustained.
- 3-Nucleoside analogue reverse transcriptase inhibitor (NRTI) regimen with abacavir + tenofovir + lamivudine: In a randomized trial for treatment naïve patients, patients randomized to this regimen showed a significantly high rate of "early virologic non-response" in patients when compared to patients treated with efavirenz + abacavir + lamivudine. This combination should not be used as a 3-NRTI regimen in treatment-naïve or experienced patients.
- 3-NRTI regimen with didanosine + tenofovir + lamivudine: In a small pilot study, a high rate (91%) of virologic failure was seen in treatment–naïve patients initiated on this 3-NRTI regimen. This combination should not be used as a 3-NRTI regimen in treatment-naïve or experienced patients.
- Didanosine (ddI) + stavudine (d4T): The combination of ddI and d4T can result in a high incidence of toxicities, particularly peripheral neuropathy, pancreatitis, and lactic acidosis. This combination has been implicated in several deaths in HIV-1 infected pregnant women secondary to severe lactic acidosis with or without hepatic steatosis and pancreatitis after prolonged use of regimens containing these two agents in combination. In general, combinations containing didanosine and stavudine should be used only when other NRTI drug combinations have failed or have caused unacceptable toxicities, where potential benefit outweighs the risks of toxicities.
- Zidovudine plus stavudine: Combination regimens containing these two NRTIs should be avoided due to the demonstration of antagonism in vitro and in vivo.

- Saquinavir hard gel capsule (Invirase®) as a single protease inhibitor (PI): The hard gel formulation of saquinavir is contraindicated as a single PI due to poor bioavailability that averages only 4% even with a concurrent high-fat meal.
- Zalcitabine plus stavudine or zalcitabine plus didanosine: These combinations are contraindicated due to increased rates and severity of peripheral neuropathy.
- Atazanavir plus indinavir: Both of these protease inhibitors can cause grade 3 to 4 hyperbilirubinemia and jaundice. Additive or worsening of these adverse effects may be possible when these agents are used concomitantly.
- Emtricitabine plus lamivudine as 2 NRTI backbone: Both drugs have similar resistance profiles and minimal additive antiviral activity.

QUALIFYING STATEMENTS

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- The recommendations are not intended to substitute for the judgment of a clinician who is an expert in the care of human immunodeficiency virus (HIV)-infected individuals.
- Although the guidelines represent the state of knowledge regarding the use of antiretroviral agents, this is an evolving science and the availability of new agents or new clinical data regarding the use of existing agents will change therapeutic options and preferences.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Department of Health and Human Services, Henry J. Kaiser Family Foundation. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and

adolescents. Bethesda (MD): Department of Health and Human Services, Henry J. Kaiser Family Foundation; 2004 Mar 23. 97 p. [355 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1998 Dec 1 (revised 2004 Mar 23)

GUIDELINE DEVELOPER(S)

Centers for Disease Control and Prevention - Federal Government Agency [U.S.]
Department of Health and Human Services (U.S.) - Federal Government Agency [U.S.]
Henry J. Kaiser Foundation - Private Nonprofit Organization

SOURCE(S) OF FUNDING

United States Government

GUIDELINE COMMITTEE

Panel on Clinical Practices for Treatment of HIV Infection

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

These guidelines were developed by the Panel on Clinical Practices for Treatment of HIV Infection convened by the Department of Health and Human Services (DHHS).

Leadership of the Panel consists of Anthony S. Fauci (co-chair) and John G. Bartlett (co-chair)

Current members of the Panel include: Jean Anderson; A. Cornelius Baker; Samuel A. Bozzette; Charles Carpenter; Martin Delaney; Lawrence Deyton; Wafaa El-Sadr; Courtney Fletcher; Gregg Gonsalves; Eric P. Goosby; Fred Gordin; Roy M. Gulick; Mark Harrington; Martin S. Hirsch; John W. Mellors; James Neaton; Robert T. Schooley; Renslow Sherer; Stephen A. Spector; Sharilyn K. Stanley; Paul Volberding; Suzanne Willard

Participants from the Department of Health and Human Services include: Debra Birkrant; Victoria Cargill; Laura Cheever; Mark Dybul; Jonathan Kaplan; Henry Masur; Lynne Mofenson; Jeffrey Murray; Alice Pau

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline. It was last updated on March 23, 2004.

The Antiretroviral Working Group, a subgroup of the Panel, meets monthly to review new data; recommendations for changes in this document are then submitted to the Panel and incorporated as appropriate. The most recent information is available on the AIDSinfo Web site.

Status information regarding this guideline is available from the AIDSinfo Web site, telephone (800) 448-0440, fax (301) 519-6616; TTY (888) 480-3739.

GUIDELINE AVAILABILITY

Electronic copies: Available from the AIDSinfo Web site and the National Library of Medicine's HSTAT database.

Print copies: Available from the Centers for Disease Control and Prevention, National Prevention Information Network (NPIN), P.O. Box 6003, Rockville, MD 20850. Telephone: (800) 458-5231, TTY (800)-243-7012 International number (301)-562-1098. Web site: www.cdcnpin.org. Requests for print copies can also be submitted via the AIDSinfo Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Report of the NIH Panel to Define Principles of Therapy of HIV Infection and Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents. MMWR Morb Mortal Wkly Rep 1998 Apr 24;47(RR-5):43-82.
- Considerations for antiretroviral therapy in women. In: Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Bethesda (MD): Department of Health and Human Services, Henry J. Kaiser Family Foundation; 2002 Feb 4. pp. 75-6. Available in Portable Document Format (PDF) from the AIDSinfo Web site.
- Hydroxyurea. In: Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Bethesda (MD): Department of Health and Human Services, Henry J. Kaiser Family Foundation; 2002 Feb 4. pp. 77. Available in Portable Document Format (PDF) from the AIDSinfo Web site.
- Safety and toxicity of individual antiretroviral agents in pregnancy. 2001 Jan 24 (updated 2004 Jun 23). pp. 78-93. Available in Portable Document Format (PDF) from the AIDSinfo Web site.

Print copies: Available from the Centers for Disease Control and Prevention, National Prevention Information Network (NPIN), P.O. Box 6003, Rockville, MD 20850. Telephone: (800) 458-5231, TTY (800)-243-7012 International number (301)-562-1098. Web site: www.cdcnpin.org. Requests for print copies can also be submitted via the AIDSinfo Web site.

The following is also available:

- Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents tool for Palm OS* or Pocket PC PDA. The download is available from the AIDSinfo Web site.

PATIENT RESOURCES

The following is available:

- HIV and Its Treatment: What You Should Know (English or Spanish) - May 2004.

Electronic copies: Available from the AIDSinfo Web site.

Print copies: Available from the Centers for Disease Control and Prevention, National Prevention Information Network (NPIN), P.O. Box 6003, Rockville, MD 20850. Telephone: (800) 458-5231, TTY (800)-243-7012 International number (301)-562-1098. Web site: http://www.cdcnpin.org. Requests for print copies can also be submitted via the AIDSinfo Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This summary was completed by ECRI on July 20, 1999. The original information was verified by the guideline developer on August 10, 1999. Updated guidelines were issued on January 28, 2000, February 5, 2001, April 23, 2001, August 17, 2001, February 4, 2002, July 14, 2003, November 10, 2003, and November 17, 2003. This summary was most recently updated on March 29, 2004.

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